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Influence of Preoperative Transarterial Lipiodol Chemoembolization on Resection and Transplantation for Hepatocellular Carcinoma in Patients With Cirrhosis

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Objective

To investigate the impact of preoperative transarterial lipiodol chemoembolization (TACE) in the management of patients undergoing liver resection or liver transplantation for hepatocellular carcinoma.

Patients and Methods

TACE was performed before surgery in 49 of 76 patients undergoing resection and in 54 of 111 patients undergoing liver transplantation. Results were retrospectively analyzed with regard to the response to treatment, the type of procedure performed, the incidence of complications, the incidence and pattern of recurrence, and survival.

Results

In liver resection, downstaging of the tumor by TACE (21 of 49 patients [42%]) and total necrosis (24 of 49 patients [50%]) were associated with a better disease-free survival than either no response to TACE or no TACE (downstaging, 29% *vs.* 10% and 11% at 5 years, $p = 0.08$ and 0.10; necrosis, 22% *vs.* 13% and 11% at 5 years, $p = 0.1$ and 0.3). Five patients (10%) with previously unresectable tumors could be resected after downstaging.

In liver transplantation, downstaging of tumors >3 cm (19 of 35 patients [54%]) and total necrosis (15 of 54 patients [28%]) were associated with better disease-free survival than either incomplete response to TACE or no TACE (downstaging, 71% *vs.* 29% and 49% at 5 years, $p = 0.01$ and 0.09; necrosis, 87% *vs.* 47% and 60% at 5 years, $p = 0.03$ and 0.14). Multivariate analysis of the factors associated with response to TACE showed that downstaging occurred more frequently for tumors >5 cm.

Conclusions

Downstaging or total necrosis of the tumor induced by TACE occurred in 62% of the cases and was associated with improved disease-free survival both after liver resection and

transplantation. In liver resection, TACE was also useful to improve the resectability of primarily unresectable tumors. In liver transplantation, downstaging in patients with tumors >3 cm was associated with survival similar to that in patients with less extensive disease.

Hepatocellular carcinoma (HCC) is a major health concern worldwide, with an incidence of approximately 1 million cases a year. In the Western world, the current epidemic of cirrhosis due to the hepatitis C virus, with a ratio of malignant transformation of 2% to 8% per year, is leading to a steady increase in the number of new cases.[1] For patients with early disease, surgery, in the form of liver resection or liver transplantation, is the most effective form of treatment. Unfortunately, in patients with large or multiple tumors (still the majority, despite the increasing diffusion of screening programs), the results are much worse, with a median survival as poor as 10 months.[2] Liver resection and transplantation can therefore be offered with a good chance of success to only a small number of patients, and there is a need for associated treatments to improve the resectability rate and to diminish the incidence of recurrence after surgery.

Transarterial chemoembolization (TACE) is a procedure involving the injection of lipiodol (iodized poppyseed oil) and a chemotherapeutic agent into the hepatic artery, followed by embolization with absorbable gelatin particles. The intent is to produce a selective ischemic and pharmacologic injury to the tumor, which relies mainly on the arterial circulation (as opposed to the rest of the liver, which is also perfused by the portal flow). A further effect is that lipiodol persists in the tumor tissue and is easily detectable by computed tomography (CT scan) carried out 3 to 5 weeks after the procedure. Small tumors that may have escaped detection can then be identified, allowing more accurate staging of the disease.

TACE was introduced as a palliative treatment for patients with inoperable disease. Good results were reported in many retrospective series[3–8]; a less clear advantage was found in more recent prospective studies.[9–11] The role of TACE as preoperative treatment for patients undergoing liver resection for HCC has been investigated in some studies with conflicting results,[12–15] mainly concerning the increased occurrence of extrahepatic metastases[16] and of hepatic or perihepatic recurrence.[17] Although many units use TACE in patients before liver transplantation for HCC,[18,19] only one report is available on the effect of this treatment.[20]

The aim of this study was to review the experience with TACE in a cohort of patients undergoing liver resection or transplantation for HCC, particularly with regard to the impact on disease-free survival, and to outline the role of TACE in the management of these patients.

PATIENTS AND METHODS

In the 11-year period between January 1985 and December 1995, 207 patients in our unit underwent operative treatment for histologically confirmed HCC associated with cirrhosis.

Liver Resection

From 85 patients undergoing liver resection, 9 patients were excluded because the surgical procedure was macroscopically noncurative (4 patients) or because other methods of tumor ablation (*e.g.*, alcohol injection or cryosurgery) were associated with surgical excision (5 patients). The characteristics of the 76 patients retained in the study population are shown in Table 1.

The technique of liver resection for HCC with cirrhosis in our unit has been standardized since 1984.[21] Liver function was evaluated before surgery with a modification of the Child score[22] and indocyanine green clearance to indicate the extent of liver resection that could be safely undertaken. At operation, exploration of the abdominal cavity was performed to detect any extrahepatic spread. Enlarged hepatic and celiac lymph nodes were excised for frozen-section histology. Systematic liver ultrasound was carried out and any suspicious nodule was biopsied. In most cases, if three or more intrahepatic tumor nodules were found, or if there was evidence of extrahepatic spread, the resection was not undertaken. The technique of hepatectomy involved ultrasound-guided segmental or subsegmental excision with preliminary control of the portal pedicle.[23,24] Postoperatively, adjuvant chemotherapy was not given due to the adverse effects of anticancer drugs on the underlying cirrhosis.

Liver Transplantation

During the study period, liver transplantation was performed in 125 patients with histologically confirmed HCC associated with cirrhosis. Three patients with incomplete removal of the tumor were excluded from this study. Transarterial lipiodol chemotherapy without embolization was performed in 11 patients, who were excluded from the analysis, leaving 111 patients who represent the population of transplanted patients considered in this study. The indications for liver transplantation for HCC have been reported previously.[25] Briefly, liver transplantation

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Table 1. RESECTION: POPULATION AND TUMOR CHARACTERISTICS (76 PATIENTS)

	TACE	No TACE	p
Number of patients	49 (64%)	27 (36%)	
Age (yr)	59.2 ± 7.1	60.9 ± 7.8	NS
Males/females	44/5 (90%)	26/1 (96%)	NS
Child score			
A	43 (88%)	17 (63%)	0.01
B	6 (12%)	10 (37%)	NS
C	—	—	
Alcohol	10 (20%)	17 (63%)	0.001
Hepatitis B	10 (20%)	6 (22%)	NS
Hepatitis C	16 (33%)	1 (4%)	0.02
Other	13 (28%)	3 (11%)	0.08
α-Fetoprotein	285 ± 1629	129 ± 250	0.5
Initial tumor size (cm)	5.05 ± 2.53	3.95 ± 1.89	0.05
<3 cm (number of patients)	12 (24%)	14 (52%)	0.03
3–5 cm	20 (41%)	6 (22%)	0.05
>5 cm	17 (34%)	7 (26%)	NS
Tumor number (mean ± SD)	1.35 ± 0.88	1.3 ± 0.5	NS
1 nodule	39 (80%)	20 (74%)	NS
2 nodules	6 (12%)	6 (23%)	NS
3 nodules	3 (6%)	1 (4%)	NS
4 nodules	1 (3%)	1 (3%)	
Vascular thrombus	4 (8%)	1 (4%)	0.6
TACE (number of courses)	2.0 ± 0.8		
1 (number of patients)	18 (37%)		
2	19 (39%)		
≥3	12 (24%)		
Postoperative chemotherapy	3 (6%)	—	
(mean number of courses)	(4)	—	

TACE = transarterial chemoembolization; NS = not significant.

for HCC is performed for patients with no evidence of extrahepatic disease. In 80 patients, HCC was discovered on routine screening of well-compensated cirrhosis, and cancer represented the main indication for transplantation (known tumors). In 11 patients, a tumor nodule was discovered during the pretransplant evaluation for decompensated cirrhosis and hepatic failure (incidental tumors). In 20 patients, the tumor was discovered on the hepatectomy specimen (unknown tumors). Patients with unknown tumors were included in the analysis because patient survival was identical to the survival of patients with known tumors of equal size and number, and the biologic behavior of the tumor was unlikely to be different. Patient characteristics are shown in Table 2.

The operation was started with a limited incision to look for evidence of extrahepatic disease, considered a contraindication for transplantation. Lymph nodes in the hepatic pedicle (and in the celiac region if enlarged) were sampled for frozen-section examination. To decrease the risk of disseminating tumor cells during manipulation of the liver, the cell-saver was not used. To avoid dislodging intrahepatic thrombi during aspiration of the portal trunk, extracorporeal bypass was used only after clamping of the distal portal vein. After transplantation, routine immunosuppression was used and adjuvant chemotherapy with doxorubicin (Adriamycin) and 5-fluorouracil was given for a total of nine cycles as soon as—and if—the patient's general condition allowed it.

Transarterial Lipiodol Chemotherapy

This was performed as part of the preoperative treatment for 49 of 76 patients (63%) in the resection group and 54 of 111 patients (49%) in the transplantation group. TACE was introduced in our unit in 1984 and has been used systematically in patients undergoing liver resection or transplantation for HCC since 1988. The aims of treatment were accurate staging of intrahepatic disease, reduc-

Table 2. TRANSPLANTATION: POPULATION AND TUMOR CHARACTERISTICS (111 PATIENTS)

	TACE	No TACE	p
Number of patients	54	57	
Age (yr)	54 ± 7.6	50.1 ± 8.6	0.02
Sex (M/F)	51/3	44/13	0.01
Child score			
A	25 (47%)	10 (18%)	0.001
B	23 (43%)	20 (35%)	NS
C	5 (9%)	27 (47%)	0.0001
Alcohol	1 (2%)	3 (5%)	NS
Hepatitis B	7 (14%)	15 (26%)	0.09
Hepatitis C	30 (60%)	18 (32%)	NS
Hepatitis B + C	4 (8%)	6 (11%)	NS
Other	8 (16%)	15 (26%)	NS
α-Fetoprotein	1459 ± 4165	128 ± 288	0.04
Tumor size (radiology)	4.7 ± 2.3	3.8 ± 2.3*	0.07
≤3 cm (number of patients)	19 (35%)	17 (46%)*	NS
>3–5 cm (number of patients)	20 (37%)	13 (35%)*	NS
>5 cm (number of patients)	15 (28%)	7 (19%)*	NS
Tumor number (radiology)	2.0 ± 1.6	2.0 ± 1.2*	NS
≤3 nodules	30 (56%)	17 (46%)*	NS
>3–5 nodules	10 (19%)	7 (19%)*	NS
>5 nodules	14 (26%)	13 (35%)*	NS
Vascular thrombus (rad)	7 (18%)	4 (17%)*	NS
TACE (number of courses)	1.96 ± 1.49		
1 (number of patients)	28 (53%)		
2	12 (23%)		
≥3	13 (25%)		
Postoperative chemotherapy courses (SD)	27/52 (52%) 6.7 ± 2.5	16/45 (36%) 6.6 ± 3.6	0.11 NS

TACE = transarterial chemoembolization; NS = not significant.
* Includes only patients with known tumors (N = 37).

tion in the size of the tumor to increase resectability or to diminish the extent of the hepatectomy, and exploration of a possible benefit on survival.

TACE was performed in the absence of contraindications. Poor liver function, the most common contraindication to TACE, was underrepresented among patients undergoing resection because good liver functional capacity was a prerequisite in this group. In the transplantation group, most of the patients who did not undergo TACE were in the Child's class C or had unknown tumors. If TACE was well tolerated, it was repeated every 2 to 3 months until a donor organ became available.

Conventional mesenteric arteriography was performed first to check for the presence of a right hepatic artery and to outline the portal circulation in the venous phase films. The celiac artery was catheterized next, and after assessment of the hepatic vascular anatomy a mixture of 10 mL of lipiodol (Lipiodol Ultrafluide; Guerbet, Aulnay-sous-Bois, France) and doxorubicin (Adriamycin; Farmacia, Saint-Quentin-en-Yvelines, France) 50 mg or cisplatin (Cisplatyl; Lilly, St. Cloud, France) 50 to 70 mg was given. Embolization was performed with gelatin sponge powder until April 1989 and gelatin pellets (Gelfoam; Upjohn, Kalamazoo, Michigan) thereafter. No attempt was made to perform a selective injection of the tumor vascular bed because part of the effect sought with TACE was to highlight tumor nodules undetected by ultrasound and CT. CT scanning was performed 4 weeks after TACE to show lipiodol uptake by the tumor tissue.

Histopathologic and Radiologic Studies

Surgical specimens and total hepatectomy specimens were examined for features of the tumor disease, such as size and number of nodules, portal vein thrombosis, distance from the surgical margin, necrosis (defined as complete if no viable cells were found on all nodules), and the presence of an intact capsule, of satellite nodules, and of vascular invasion. Tumor size and number were measured on preoperative ultrasound or CT after the cancerous nature of the target was confirmed by histologic examination. The size of the nodule on the surgical specimen was taken as the final size in all patients after confirming that this measurement was identical to the size on ultrasound examination (if this had been performed shortly before the operation). A significant reduction in tumor size (downstaging) was defined as a 50% reduction of the product of the perpendicular diameters of the largest lesion.[26]

Follow-Up

Patients were followed up in the outpatient clinic with ultrasound, liver function tests, and alpha-fetoprotein measurements every 3 months and abdominal and chest CT scans every 6 months. Three patients in the resection group with known recurrences were lost to follow-up and were considered dead at the time of the last outpatient attendance. Two patients in the resection group who later underwent transplantation for deteriorating liver function with no recurrence were considered alive with no recurrence at the time of transplantation. The objective of the study was to analyze the incidence of operative and postoperative complications, the incidence and pattern of recurrence, and patients' overall and disease-free survival.

Table 3. RESECTION: RESULTS

	TACE	No TACE	p
Number of patients	49	27	
Interval diagnosis–operation	7.9 ± 6.3	2.2 ± 2.0	<0.001
Downstaging*	21 (43%)	0%	<0.001
Type of resection			
≤1 segment	34 (69%)	19 (70%)	
2 segments	5 (10%)	8 (30%)	0.009
≥3 segments	10 (21%)	0	
Blood transfusion	2.6 ± 2.9	5.6 ± 12.2	NS
Operative mortality	0	0	
Postoperative complications	50%	65%	NS
Liver related	41%	52%	NS
Postoperative mortality (60 days)	2 (4%)	2 (7%)	NS
Histology			
Total necrosis	24 (50%)	1 (4%)	<0.001
Capsule intact	37%	44%	NS
Vascular invasion	31%	53%	NS
Satellite nodules	33%	14%	NS
Resection margin			
<1 cm	6 (9%)	7 (23%)	
>1 cm	39 (87%)	19 (73%)	NS
Median follow-up (mo)	25.8	30.8	NS
Recurrence	28 (57%)	22 (81%)	0.01
Liver	25 (51%)	20 (74%)	
Liver local	6	8	
Liver distant	19	12	
Pulmonary	2 (4%)	—	
Unknown	—	2 (7%)	
Survival–disease-free survival (%)			
1 yr	84–61	78–63	
3 yr	57–29	47–26	NS
5 yr	43–18	35–11	
Late mortality unrelated to HCC	4	4	

TACE = transarterial chemoembolization; HCC = hepatocellular carcinoma; NS = not significant.
* 50% reduction in the product of the maximum diameters of the tumor.

Statistical Analysis

We used a biomedical statistical program (Statistica 4.0; Statsoft, Tulsa, OK). Continuous variables were com-

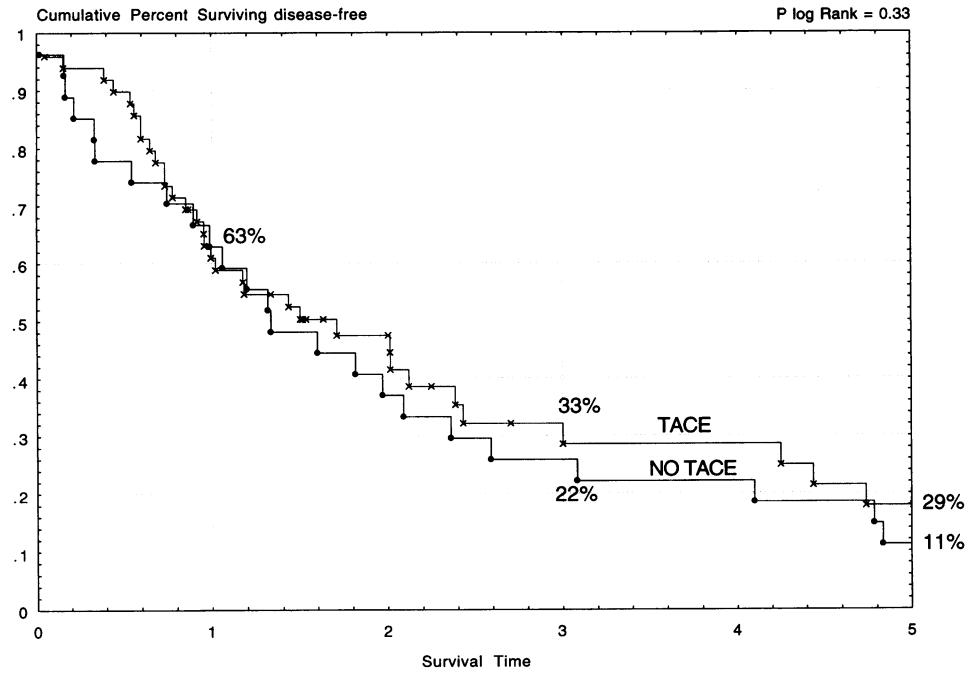

Figure 1. Cumulative disease-free survival after liver resection for hepatocellular carcinoma associated with cirrhosis. Transarterial chemoembolization (TACE: n = 49 patients) and non-TACE (n = 27 patients).

pared with the Mann Whitney U test when the variance was unequal in the two groups and with Student's t test otherwise. Contingency analysis was performed with the chi square test or with Fisher's exact test for fewer than five observed events. The Kaplan-Meier method was used to calculate survival, and groups were compared with the log rank test. Multivariate analysis was performed with a multiple logistic regression model integrating 7 of 21 variables that were found to approach or reach statistical significance on univariate analysis. A p value <0.05 was considered to be statistically significant.

RESULTS

Resection

The TACE and non-TACE populations differed in the incidence of alcoholic cirrhosis and in the incidence of

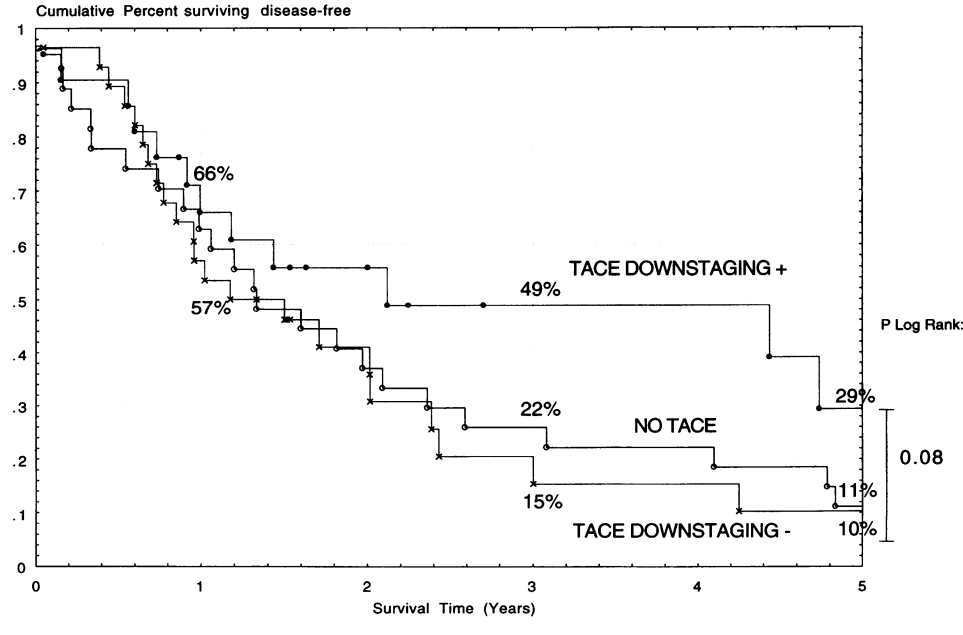

Figure 2. Cumulative disease-free survival after liver resection: downstaging of the lesion by TACE (downstaging positive: n = 21 patients), no response to TACE (downstaging negative: N = 28 patients), and no TACE (n = 27 patients).

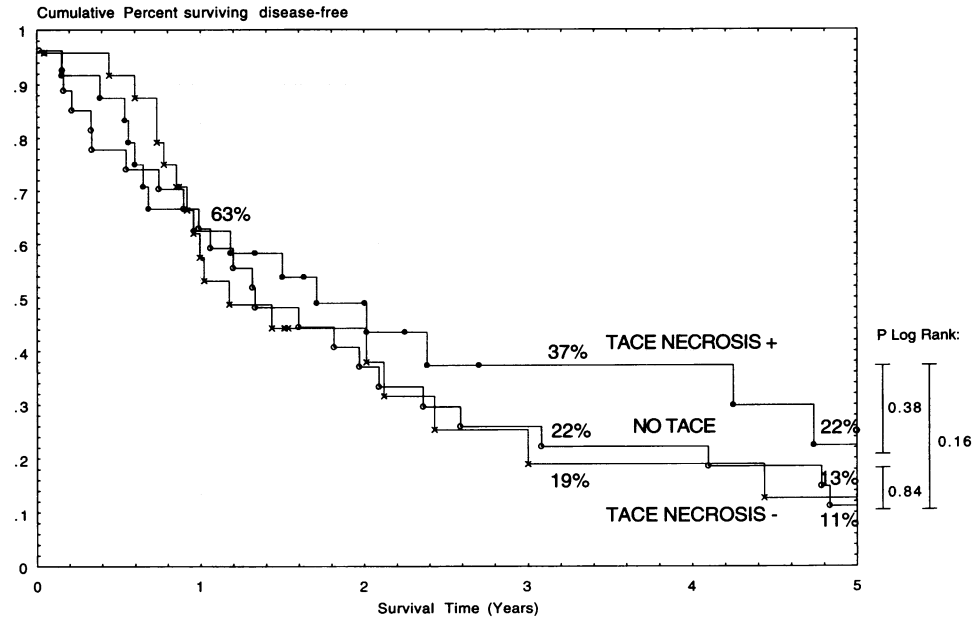

Figure 3. Cumulative disease-free survival after liver resection: complete necrosis of the lesion by TACE (necrosis positive: n = 24), no necrosis after TACE (necrosis negative: n = 25), and no TACE (n = 27).

cirrhosis related to the hepatitis C virus. The mean size of tumors was larger in patients with TACE, although this did not quite reach statistical significance (see Table 1). The interval between diagnosis and surgery was significantly longer for patients undergoing TACE (see Table 2). Downstaging of the tumor after TACE was observed in 21 (44%) of the patients, as opposed to no patients when TACE was not performed. Five patients of 49 (10%) with tumors previously considered unresectable could undergo surgical excision after TACE.

Operative Data and Postoperative Mortality

A larger liver resection was performed in patients after TACE as compared to patients without TACE. Although patients after TACE had less blood transfusions during the perioperative period, this was not statistically significant. There were two postoperative deaths in the TACE group (hepatocellular failure and variceal hemorrhage) and two in the non-TACE group (hepatocellular failure and sepsis). The incidence of postoperative complications, divided into general surgical complications and complications representing decompensation of hepatocellular function (jaundice, ascites, or encephalopathy), was similar in the two groups.

Histology

Total necrosis of the tumor was observed in 24 (50%) of the 47 patients treated with TACE and in 1 of the patients who did not undergo TACE, who had received percutaneous ethanol injection therapy ($p < 0.001$). The incidence of unfavorable histologic features, such as capsular invasion, satellite nodules, and vascular invasion, was similar in the TACE and the non-TACE groups. The number of cases with narrow resection margins was similar in the two groups. Total necrosis was observed in 11 of 21 cases where downstaging had occurred (52%); however, 13 of 24 cases of total necrosis (54%) did not meet the size reduction criteria for downstaging.

Total Response Rate

Downstaging or necrosis occurred in 34 of 49 patients, representing 69% of the population who underwent TACE before liver resection.

Patient Survival and Disease-Free Survival

This is shown in Table 3 and in Figures 1 to 3. Overall, there was no significant difference between the TACE and the non-TACE groups. However, patients in whom TACE induced downstaging of the tumor (21 of49 [42%]) had a better disease-free survival than patients with no response to TACE (at 5 years, 29% *vs.* 10%, $p = 0.08$) or no TACE (11%, $p = 0.10$). Similarly, the induction of total necrosis by TACE was associated with improved 5-year disease-free survival, although this did not reach statistical significance ($p = 0.16$). Intrahepatic recurrence, by far the most common form (92% of first recurrences in both groups), was in most cases (80% in the TACE group, 74% in the non-TACE group) at a distance from the site of the original surgery. Recurrence presenting first at an extrahepatic site was not observed in the non-TACE group and occurred in 2 patients after TACE (4%), 1 with a 10-cm tumor and thrombi in the hepatic vein, the other with a 7.5-cm tumor.

Transplantation

Patients in the TACE and the non-TACE group differed in the severity of the underlying liver disease (p = 0.01), with an increased representation of Child's class C in patients not undergoing TACE (see Table 2). The interval between the diagnosis of HCC and transplantation was 7 months longer for patients undergoing TACE. Although the size of the tumors did not differ when considering only patients with known or incidental tumors (4.7 ± 2.3 *vs.* 3.8 ± 2.3, p = 0.07), 18 of the 20 patients with unknown tumors had nodules <3 cm, decreasing the mean size of tumors in the non-TACE population (4.7 ± 2.3 *vs.* 3.1 ± 2.1, p = 0.001). Downstaging, as defined above, was seen in 28 of 54 patients (51%) in the TACE group and in no patients with known tumors in the non-TACE group (p < 0.001) (Table 4).

Operative Data and Postoperative Mortality

There was no significant difference in the number of blood units transfused or in the incidence of variant arterial reconstructions (*e.g.*, anastomosis on the splenic or celiac artery or on the aorta), although post-TACE inflammatory thickening of the hepatic pedicle was commented on in two cases and TACE was considered responsible for a useless hepatic artery in three cases. There was one preoperative death in the non-TACE group (cardiac arrhythmia). Postoperative mortality (60 days from the procedure) occurred in 2 patients in the TACE group (cardiac failure and sepsis) and in 2 patients in the non-TACE group (primary nonfunction and sepsis after retransplantation in 1 patient and diffuse aspergillosis in the other). Arterial and biliary complications occurred respectively in 2 cases (3%) and in 8 cases (12%) in the TACE group and in 2 cases (4%) and in 10 cases (18%) in the non-TACE group.

Histology

Total necrosis of the tumor was observed in 15 of 54 patients (27%) after TACE and in 1 patient who had had percutaneous ethanol injection in the non-TACE group (p < 0.001). Total necrosis was observed in 13 of 28 cases (46%) where downstaging had occurred, and downstaging was observed in 13 of 15 cases (87%) of total necrosis. The incidence of satellite nodules was higher in the TACE group (37%) than in the non-TACE group (19%). The distribution of other unfavorable histologic features, such as capsular and vascular invasion, was similar in the TACE and in the non-TACE groups.

Total Response Rate

Downstaging or necrosis occurred in 30 of 54 patients (56%) who underwent TACE before transplantation.

Table 4. TRANSPLANTATION: RESULTS (N = 111)

	TACE	No TACE	p
Number of patients	54	57	
Interval diagnosis–transplantation (mo)	13.1 ± 11.8	5.8 ± 3.4*	<0.001
Downstaging†	28 (52%)	—	<0.001
Blood transfusions	11.5 ± 10.8	15.9 ± 13.9	NS
Variant arterial reconstruction	9 (17%)	7 (12%)	NS
Arterial complications	0	3 (5%)	NS
Biliary complications	5 (9%)	6 (10%)	NS
Total complications	23 (43%)	18 (31%)	NS
Operative mortality	1 (2%)	1 (2%)	NS
Postoperative mortality (60 days)	1 (2%)	2 (4%)	NS
Tumor size (histology)	3.5 ± 2.2	3.1 ± 2.1	NS
≤3 cm (number of patients)	33 (61%)	37 (65%)	NS
>3–5 cm (number of patients)	13 (24%)	12 (21%)	NS
>5 cm (number of patients)	8 (15%)	8 (14%)	NS
Tumor number (histology)	3.1 ± 3.3	2.8 ± 2.6	NS
1 nodule	25 (46%)	24 (42%)	NS
2 nodules	13 (24%)	12 (21%)	NS
≥3 nodules	16 (30%)	21 (37%)	NS
Vascular thrombus (histology)	8 (17%)	6 (11%)	NS
Capsule intact	46%	45%	NS
Satellite nodules	39%	19%	0.04
Vascular invasion	38%	36%	NS
Total necrosis	15 (28%)	1 (2%)	<0.001
Median follow-up (mo)	36.5	40.0	NS
Recurrence	15 (28%)	8 (14%)	NS
Liver	3	2	
Pulmonary	5	1	
Bone	3	2	
Lymph nodes	1	2	
Adrenal	3	1	
Survival–disease-free survival (%)			
1 yr	87–78	77–74	
3 yr	65–63	69–66	NS
5 yr	55–57	62–59	
Late mortality unrelated to HCC	7	12	

TACE = transarterial chemoembolization; HCC = hepatocellular carcinoma; NS = not significant.
* Includes only patients with known tumors (N = 37).
† 50% reduction in the product of the maximum diameters of the tumor.

Patient Survival and Disease-Free Survival

Overall, there was no difference in survival between the two groups (Fig. 4). However, patients with large tumors (>3 cm) that were downstaged by TACE (19 of 35 [54%]) had a disease-free survival significantly better than patients whose tumors were not downstaged (71% *vs.* 28% at 5 years, p = 0.01) or who did not undergo TACE (49% at 5 years, p = 0.09) (Fig. 5). Among the 19 patients whose tumors were downstaged by TACE HCC-related mortality occurred in 3 patients: 2 patients initially had a tumor thrombus in a branch of the portal vein, and 1 patient had extensive multinodular disease.

Table 5. SURVIVAL: DISEASE-FREE SURVIVAL ACCORDING TO DOWNSTAGING

	Resection			Transplantation (N = 111)		
	Downstaging⁺	Downstaging⁻	No TACE	Downstaging⁺	Downstaging⁻	No TACE
	N = 3	N = 9	N = 14	N = 9	N = 10	N = 35
≤30 mm						
1 yr	67–67	100–88	72–50	89–89	90–80	86–83
3 yr		52–27	36–21	89–89	57–58	75–72
5 yr		26–13	29–0	71–71	57–58	65–66
	N = 18	N = 19	N = 13	N = 19	N = 16	N = 22
>30 mm						
1 yr	89–64*	74–37*	85–73	89–84§	81–63§	64–59‖
3 yr	67–52*	52–9*	60–33	77–79§‖	42–29§	59–55‖
5 yr	58–31*	41–9*	34–20	66–71§‖	31–29§	55–49‖
	N = 21	N = 28	N = 27	N = 28	N = 26	N = 57
ALL						
1 yr	85–66†‡	82–57†	78–63‡	89–86	85–69	77–74
3 yr	64–69†‡	51–15†	47–22‡	81–82	48–40	69–66
5 yr	56–29†‡	32–10†	35–11‡	67–70	41–40	62–59

* p = 0.03.
† p = 0.08.
‡ p = 0.10.
§ p = 0.01.
‖ p = 0.09.

Nontumor-related mortality occurred in 2 patients. Disease-free survival in this group was similar to that of patients with small tumors (≤3 cm) (70% at 5 years).

Among the 15 patients whose tumor had undergone complete necrosis, recurrence developed in 1 case (7%), and death unrelated to HCC occurred in 2 cases. The disease-free survival was significantly better in these patients (87% at 5 years) than in patients who did not show complete necrosis (47% at 5 years, p = 0.03) or who did not have TACE (60% at 5 years, p = 0.14) (Fig. 6).

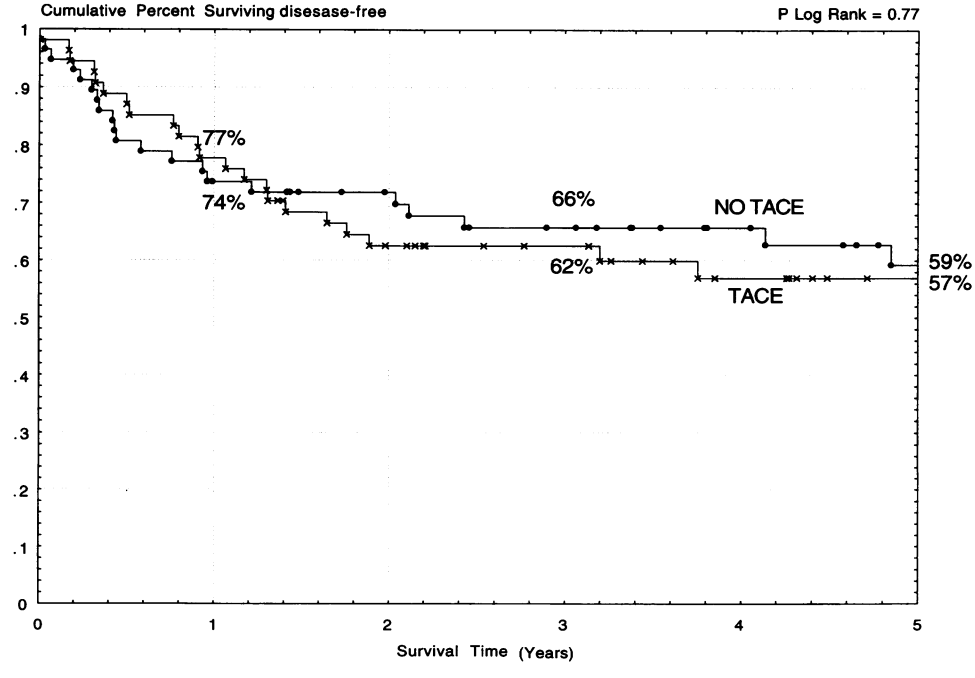

Figure 4. Cumulative disease-free survival after liver transplantation for hepatocellular carcinoma associated with cirrhosis: TACE (n = 54) and non-TACE (n = 57).

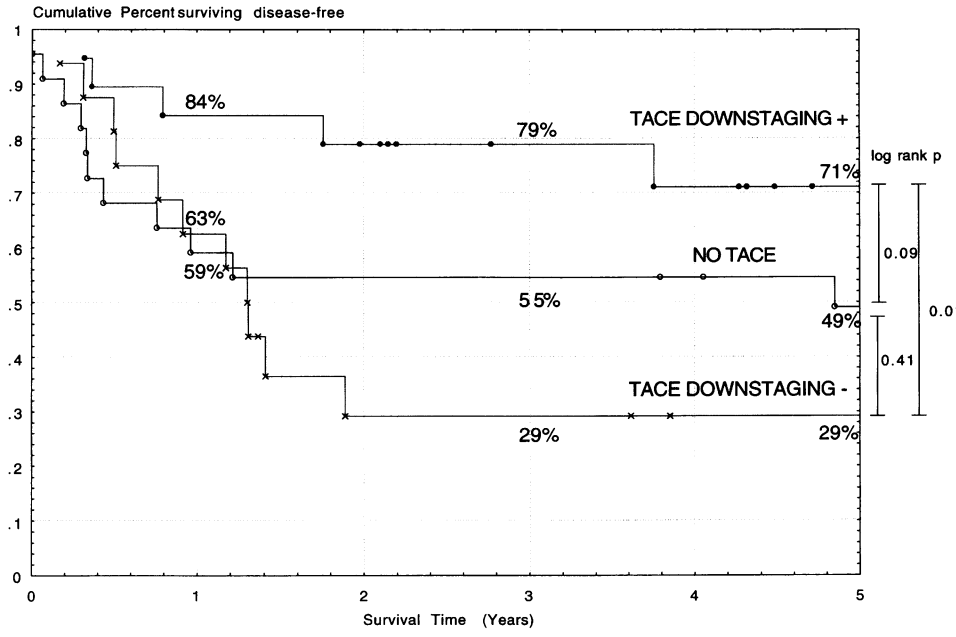

Figure 5. Cumulative disease-free survival after liver transplantation in patients with tumors >3 cm: downstaging of the lesion by TACE (downstaging positive: n = 19), no downstaging after TACE (downstaging negative: n = 16), and no TACE (n = 22).

Patients with neither downstaging nor necrosis after TACE had survival figures that were not significantly different than the figures for patients without TACE. Metastatic recurrence was higher in the TACE group (15 of 54 [28%] *vs.* 8 of 57 [16%]), but this did not reach statistical significance. Five patients had lung metastases. Four of these had extensive multinodular disease on examination of the explanted liver, and three of the five patients had a neoplastic thrombus involving the portal vein. Late death due to noncancer disease occurred in 7 patients (13%) after TACE and in 12 patients (21%) without TACE (p = 0.3).

Factors Predicting Downstaging or Necrosis

Univariate analysis of a first selection of 21 clinical or laboratory features possibly associated with downstaging or necrosis was applied to all patients who underwent TACE before resection or transplantation (103 patients) (Table 6). The five favorable variables reaching or approaching statistical significance were a Child's class A, embolization with cisplatin rather than with doxorubicin, solitary nature of the nodule, large initial size (downstag-

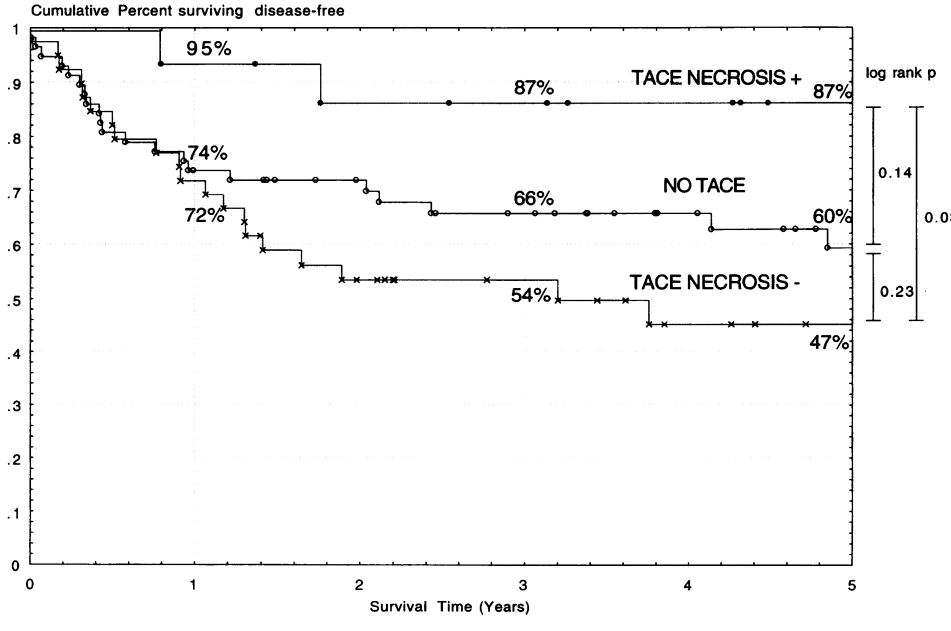

Figure 6. Cumulative disease-free survival after liver transplantation for hepatocellular carcinoma associated with cirrhosis: complete necrosis of the lesion after TACE (necrosis positive: n = 15), no necrosis after TACE (necrosis negative: n = 39), and no TACE (n = 57).

Table 6. MULTIVARIATE ANALYSIS OF FACTORS ASSOCIATED WITH DOWNSTAGING OR NECROSIS (63 PATIENTS)

Variable	Univariate p	Odd's Ratio	Multivariate p
Age	NS		
Sex	NS		
Hepatitis B	NS		
Hepatitis C	NS		
Alcohol	NS		
Child grade A	0.01–0.06†	1.00†	
Child grade B	0.03†	0.62†	0.03†
Child grade C	0.06–0.07†	0.24†	
Interval Cirrhosis–HCC	NS		
Interval HCC–surgery	NS		
TACE number of cures	NS		
No embolization			
Drug type	0.007†		
Adriamycin		1.00†	
Cisplatin		2.01–3.08†	0.07†
AFP	NS		
Tumor size	0.29*		
≤3 cm		1.00	
3–5 cm		1.61	
>5 cm		3.13	0.05*
Tumor number	0.04*		
1 nodule		1.00	
2 nodules		0.40	
≥3 nodules		0.46	
PV thrombosis	0.03*	0.16	0.03*

AFP = α-fetoprotein; PV = portal vein; HCC = hepatocellular carcinoma.
* Downstaging.
† Necrosis.

ing only), and absence of portal vein thrombosis. After multivariate analysis, the features reaching statistical significance for downstaging were initial size <5 cm (odds ratio 3.13, p = 0.05) and portal vein thrombosis (odds ratio 0.16, p = 0.03). For total necrosis, the significant features were a Child's class C (odds ratio 0.24, p = 0.03) and the use of cisplatin rather than doxorubicin (odds ratio 3.51, p = 0.04).

Separate analysis of the 11 patients who underwent only transarterial lipiodol chemotherapy without embolization before transplantation showed that only 1 patient was downstaged after this procedure, as opposed to 28 of 54 patients with embolization (p = 0.01).

DISCUSSION

In this study, we investigated the influence of TACE in patients undergoing liver resection or transplantation for HCC associated with cirrhosis. Response to TACE in the form of downstaging or total necrosis of the tumor was observed in 67% of patients undergoing resection and in 49% of patients undergoing transplantation and was associated with increased disease-free survival.

The proportion of patients responding to TACE in our population is similar to what has been found previously by other investigators.[12,20] Analysis of the factors associated with response to treatment showed that both downstaging and total necrosis of the tumor occurred more frequently in patients with solitary lesions. This is in agreement with previous reports.[20,27] Downstaging occurred more frequently in patients with tumors >5 cm, which goes against the commonly held belief that TACE is ineffective in patients with large tumors.[10,11,28] In fact, most of these studies evaluated the effect of palliative TACE in patients with inoperable disease rather than in a preoperative setting. Other investigators have reported marked size reduction after TACE in patients with large tumors.[8,12]

The choice of cytotoxic agent was also important: doxorubicin was associated with significantly less necrosis than cisplatin, confirming the results of a previous randomized trial.[4] Doxorubicin is no longer used in our center unless contraindications to the use of cisplatin, such as renal failure, are present.

The impact of preoperative treatment with TACE was different for patients undergoing resection or transplantation and is best discussed separately.

Resection

In the overall group of patients undergoing liver resection for HCC, treatment with TACE did not significantly improve the survival or decrease the incidence of recurrence. Patients whose tumors were downstaged, however (21 of 49 [43%]), had a better disease-free survival than nonresponders or untreated patients. Downstaging was more common in patients with large tumors, and it is in these patients that TACE is probably most useful.

The advantage of the response to TACE on survival was more evident at the 3- and 4-year marks than later in the follow-up (see Figs. 2 and 3). This probably reflects the adverse influence of the progression of the underlying cirrhosis and the tendency of the diseased liver to produce new cancerous foci, rather than inadequate control of the primary tumor. In our study, this is well demonstrated by the low incidence of recurrence at the site of previous surgery (as opposed to elsewhere in the liver) and by the far superior results of liver transplantation as compared to liver resection. It also may explain the lack of significant advantage for TACE in other studies taking long-term recurrence as an end point.[12,15,16] Other approaches addressing the issue of *de novo* carcinogenesis in the cir-

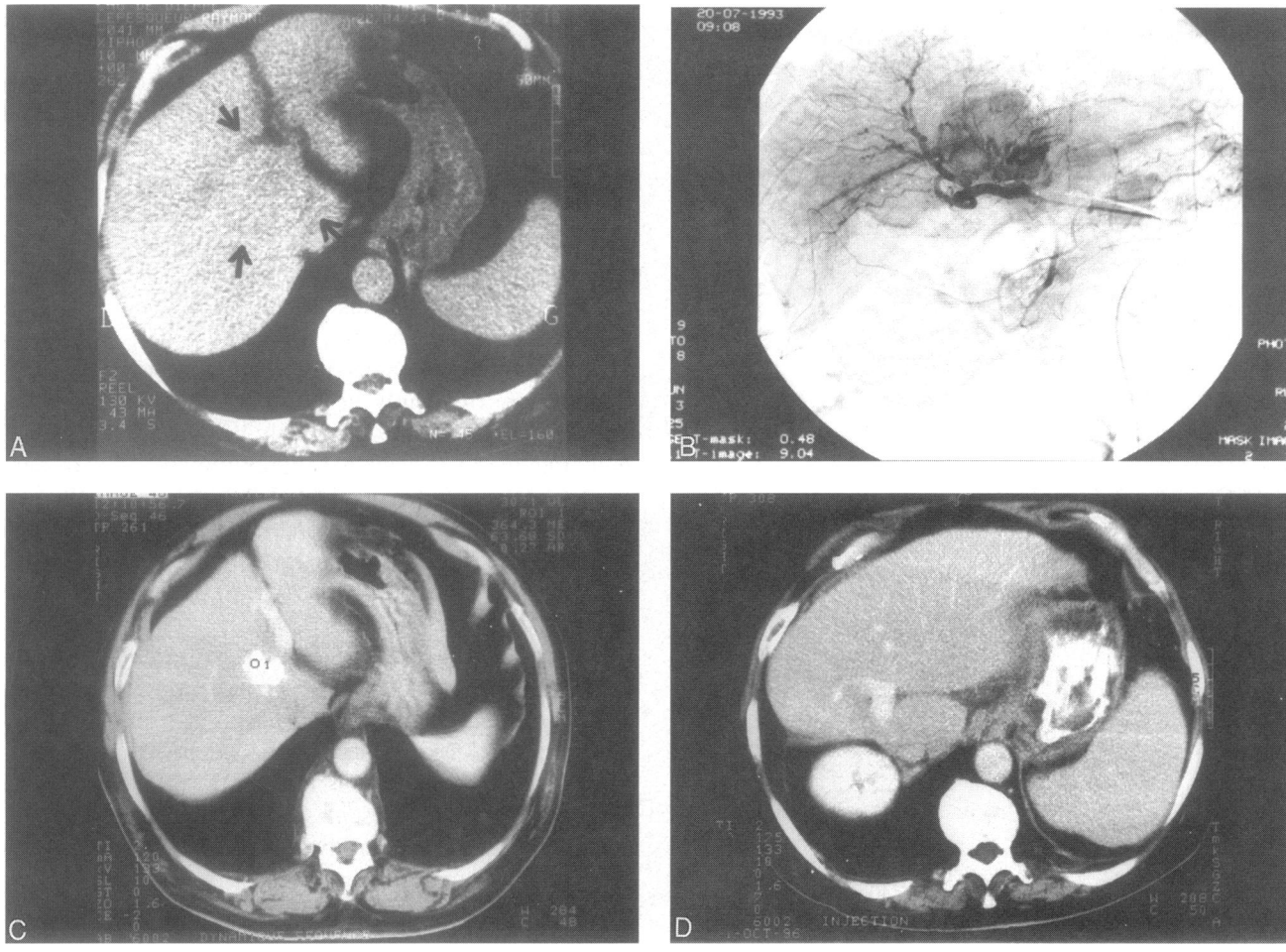

Figure 7. A 68-year-old man with alcohol-induced cirrhosis presented in April 1993 with a 5-cm tumor involving segments 5 and 8 (A), appearing as a hypervascular lesion on arteriography (B). Tumor size was reduced to 3 cm after 3 courses of TACE (C). The patient underwent a right portal vein embolization in January 1995 and an extended right hepatectomy in February 1995 (D). The patient is alive with no recurrence 2 years after hepatectomy.

rhotic liver, such as postoperative TACE[29,30] or the use of substances such as polyprenoic acid,[31] have shown promise and may represent the best way to ameliorate the results of liver resection for HCC.

TACE can show accurately tumor nodules ignored by CT scan and ultrasonography, contributing to accurate staging of the disease[32–34] and diminishing the risk of incomplete disease removal in patients undergoing resection. Furthermore, reduction of the size of the tumor may allow a decrease in the extent of the hepatectomy, a valuable advantage in patients with cirrhosis. Both these aspects, although important in our experience, cannot be properly quantified within the limits of the present investigation. Downstaging after TACE was useful in patients in whom reduction in the size of the tumor allowed us to perform surgery; in these patients, the disease had previously been considered unresectable (Fig. 7). This occurred in 10% of our patients, and a rate of secondary resectability after TACE as high as 33% has been reported in a Chinese study.[35] The incentive for secondary resection in our population may have been higher if liver transplantation had not been an option in our unit. In this context, TACE must be considered, together with other modalities of tumor destruction and with portal vein embolization, as part of the armamentarium of modern liver surgery to increase the resectability rate of malignant tumors.[36–38]

Liver Transplantation

When considering the overall group of patients undergoing liver transplantation for HCC, preoperative TACE did not appear to improve survival. However, analysis of the results for patients stratified for tumor size, the main factor associated with the risk of recurrence in our experience and in the experience of other authors,[19,25,39–45] shows

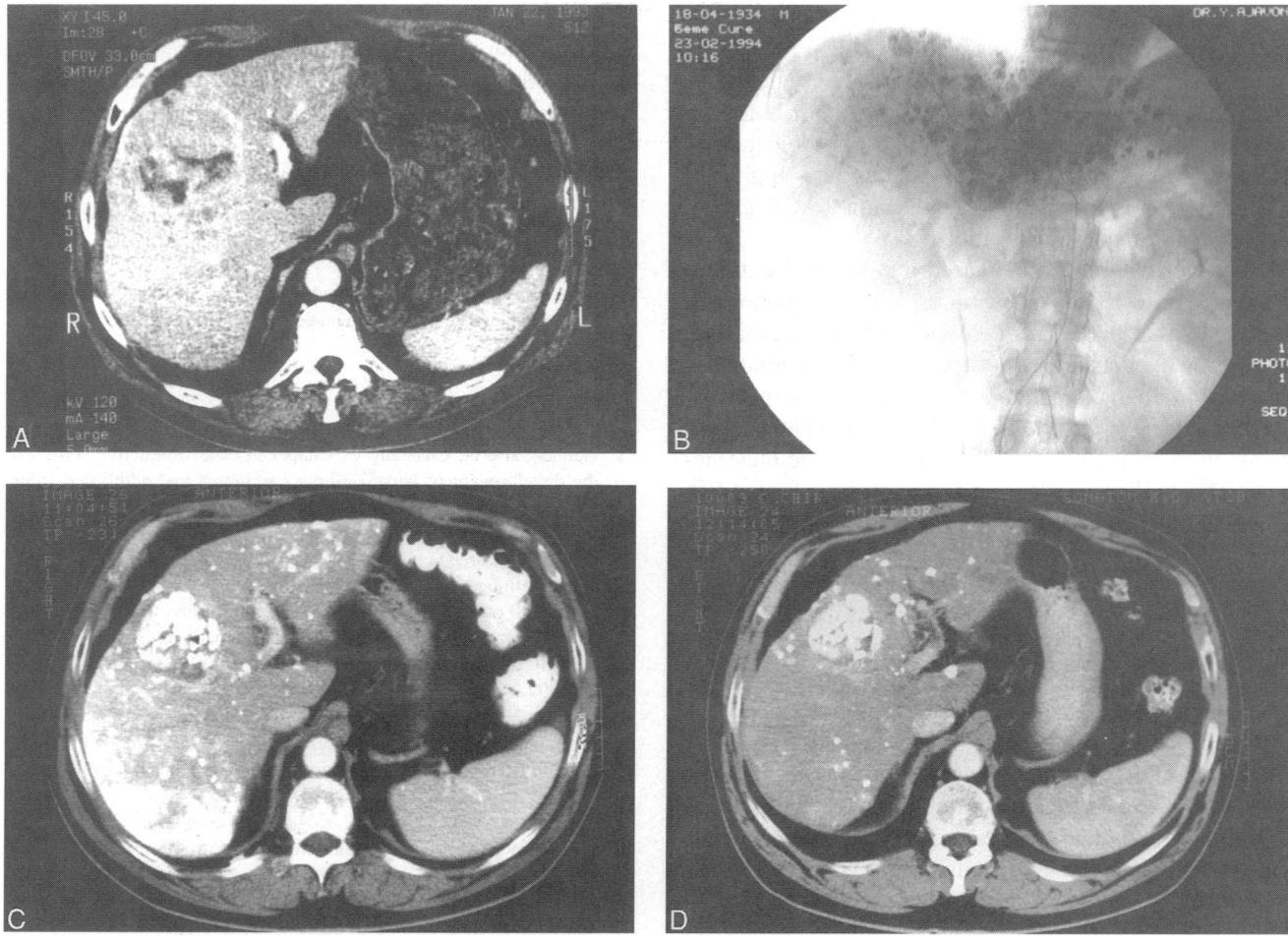

Figure 8. A 58-year-old man with alcohol-induced cirrhosis presented in April 1993 with a 9.4-cm hepatocellular carcinoma associated with multiple satellite nodules (A). Such extensive disease was initially considered unsuitable for liver transplantation. The patient had 6 courses of TACE (B) with downstaging of the tumor to 4.5 cm (C and D). Note the lipiodol uptake by the multiple small nodular lesions that were not visible on the initial computed tomography scan. Transplantation was performed in March 1994. Histologic examination of the specimen showed subtotal necrosis of the tumor. The patient is alive with no recurrence 3 years after transplantation.

a more complex picture. Patients with tumors >3 cm in whom downstaging occurred had a 5-year disease-free survival significantly better than patients who were not downstaged or who did not undergo TACE. Disease-free survival in this group (74% at 5 years) was as good as in patients with smaller tumors (75% at 5 years), and among the 19 patients who were downstaged, the 3 cases of recurrence were observed in the presence of concomitant adverse prognostic factors (10 tumor nodules in 1 patient, tumor thrombus in the portal vein in 2 other patients). Recurrence was also infrequent in patients in whom TACE induced complete necrosis of the tumor: the only patient with recurrence in this group had an 8-cm tumor nodule and a tumor thrombus in the portal vein.

Therefore, TACE before liver transplantation appears to be most useful in patients with tumors >3 cm. Response to TACE in these patients has important clinical implications: patients with large tumors are generally considered poor candidates for liver transplantation, especially when presenting with multinodular disease. Downstaging by TACE, which occurred in half the patients in this group, is associated with an incidence of recurrence as low as that in patients with smaller tumors and should be regarded as a strong argument to proceed to liver transplantation (Fig. 8).

TACE was well tolerated in virtually all cases, probably because poor liver function was respected as a contraindication for the procedure, and we did not observe an increased incidence in hepatocellular failure early or late after surgery, as reported by other authors.[13] A detailed description of the side effects of TACE in our unit has been reported previously.[7] The only case of severe hepato-

cellular failure was observed after the procedure was mistakenly performed in a patient with a surgical portacaval shunt; this patient had to be rescued by emergency liver transplantation. No operative difficulties attributed to TACE were encountered, and although the incidence of anastomosis on the splenic artery was slightly higher in the TACE group as compared to the non-TACE group, this was not statistically significant.

The concern about the increased incidence of extrahepatic metastases after TACE, raised by some authors on the grounds that partial necrosis of the tumor favors the shedding of neoplastic cells,[17,46] was not substantiated in our patients. In fact, patients with incomplete necrosis had a disease-free survival that was intermediate between patients with no necrosis and patients with complete necrosis. The higher incidence of metastases observed in patients after TACE (15 of 54 [28%] *vs.* 8 of 57 [14%]), although not statistically significant, can possibly be attributed to the larger initial size of tumors in this group (4.7 ± 2.3 *vs.* 3.1 ± 2.1, $p = 0.001$), to the presence of portal vein thrombosis, or to extensive multinodular disease, factors that are correlated to the increased incidence of extrahepatic spread.[47] Interestingly, among the 28 patients with downstaging, only 3 patients (one with 10 tumor nodules, the other 2 with portal vein thrombosis) died of tumor-related causes, and only 1 of the patients with total necrosis had disease recurrence. The mean delay from diagnosis to transplantation was longer in patients treated with TACE as opposed to patients without TACE; because of the short doubling time of hepatocellular carcinoma,[48] this may also have penalized patients in the TACE group. Given the retrospective design of our study, however, it is impossible to say whether patients who are likely to wait a long time before a compatible graft is available, such as patients with the less common blood groups, would benefit from TACE. A prospective randomized trial of TACE in patients who are candidates for transplantation may offer the answer to these questions.

CONCLUSIONS

TACE appears to be useful in the management of HCC associated with cirrhosis before liver resection or transplantation. TACE contributes to accurate staging of the intrahepatic disease, and response to treatment with downstaging or total necrosis of the tumor, obtained in more than 50% of treated cases, was accompanied by a benefit in survival. In liver resection, TACE is indicated particularly for large tumors, which are more likely to respond with downstaging, resulting in improved surgical access and resectability. In liver transplantation, TACE is useful for patients with large tumors (>3 cm) who may not initially be considered good candidates for transplantation. Response to treatment in these patients is associated with an incidence of recurrence as low as in patients with smaller tumors.

Acknowledgments

The authors thank Dr. Didier Samuel and Dr. Faouzi Saliba of the hepatology and intensive care unit, Drs. Paul and Michel Cauquil of the department of radiology, and Prof. M. Reynes and Dr. Mylène Sebagh of the department of pathology at Paul Brousse Hospital for their expertise and help in the management of our patients.

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Discussion

PROF. P. NEUHAUS (Berlin): Thank you very much for the privilege to discuss this outstanding paper by Drs. Majno, Adam and Bismuth. They are to be congratulated for their excellent series of liver resection and transplantation in patients with HCC in cirrhosis. Over the last 10 years they have operated on 207 patients, and 111 had chemoembolization before surgery. In 1996 another group, Harada and coworkers from Fukuoka, Japan, published a similar paper in *Annals of Surgery* about 140 hepatic resections for HCC: 105 or so of those patients underwent preoperative chemoembolization and 35 did not. Like you, Adam, and Bismuth, Harada observed total tumor necrosis in about one third of their patients and only small foci of viable cancer cells near the tumor capsule in 40% of the patients. With a similar protocol as the Paris group using doxorubicin, cisplatin, lipiodol, and microspheres, we could also achieve total or subtotal tumor necrosis in 40% of 74 patients who were not found suitable for resection or transplantation. Other reports in the literature support this finding of tumor reduction in necrosis after chemoembolization. Majno, Adam and Bismuth have shown the usefulness of chemoembolization in specific groups of patients in preparation for resection and transplantation, especially in those 40% to 50% who are downstaged or have complete remission. Puzzling is that the overall disease-free survival curves in patients with or without embolization are not different. Forty percent 2-year survival after re-